

Increased Adipose Tissue Expression of Toll-Like Receptor (TLR)-7 in Obese Individuals: Significance in Metabolic Disease

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Abstract

Purpose: Toll-like receptors (TLRs) are the innate immune receptors and some are now found to be involved in metabolic inflammation. TLR4 and TLR2 expressed on cell surface have emerged as immunometabolic receptors, however, the status of endocytic TLRs, especially TLR7 in metabolic disease remains unclear. Therefore, we investigated the adipose tissue expression of TLR7 in obese individuals.

Methods: For this purpose, biopsy samples of periumbilical (subcutaneous) fat were collected from 49 individuals classified based on body mass index (BMI) as 22 obese (BMI=34.13 ± 2.81 kg/m²), 18 overweight (BMI=28.26 ± 1.20 kg/m²), and 9 lean (BMI=22.61 ± 2.40 kg/m²) subjects. Expression of the TLR7, TLR-signaling components (MyD88, IRAK1, and TRAF6), macrophage markers (CD68 and CD11c), and inflammatory cytokine (IL-18) was determined by quantitative real-time RT-PCR. Systemic inflammatory marker (C-reactive protein) plasma concentrations were determined by commercial ELISA kit. Data were analyzed using *t*-test and Pearson's correlation (*r*).

Results: We found that TLR7 mRNA expression was significantly upregulated in obese (*P*=0.028) and overweight (*P*=0.043) as compared with lean individuals; this increase correlated with BMI (*r*=0.35 *P*=0.014) and body fat percentage (*r*=0.39 *P*=0.007). Moreover, TLR7 gene expression correlated positively/significantly with TLR signaling cascade proteins (MyD88: *r*=0.39 *P*=0.005; IRAK1: *r*=0.38 *P*=0.008), monocyte/macrophage markers (CD68: *r*=0.65 *P*<0.0001; CD11c: *r*=0.43 *P*=0.002), and inflammatory signatures (IL-18: *r*=0.53 *P*=0.0001; CRP: *r*=0.44 *P*=0.008).

Conclusion: The upregulated adipose tissue TLR7 expression in obesity is congruent with metabolic inflammatory state and may represent an immune marker in metabolic disease.

Keywords: TLR7; Obesity; Inflammation; Adipose tissue

Introduction

Over nutrition coupled with a sedentary lifestyle have fueled to the global rise of obesity in both young and adult populations [1]. Obesity is characterized by a state of chronic low-grade inflammation, called metabolic inflammation, in which activated monocytes infiltrate the expanding adipose tissue and colonize the tissue as resident adipose tissue macrophages (ATMs). A persistent inflammatory response in the adipose tissue is central to the pathogenesis of morbid obesity as well as it plays a role in related complications including insulin resistance and type-2 diabetes (T2D). The adipose tissue infiltration by macrophages also includes macrophage polarization and an immunophenotypic shift from M2 (anti-inflammatory) to M1 (pro-inflammatory) type. ATMs can be identified by surface markers including CD68, CD11b, and CD11c [2,3]. ATMs are known to express a number of proinflammatory cytokines/chemokines which may act through autocrine/paracrine mechanisms and lead to the development of insulin resistance. Among these pro inflammatory mediators, IL-18, TNF- α , and C-reactive protein (CRP) are the potential risk factors for development of T2D and other related complications [4].

Toll-like receptors (TLRs) are the evolutionarily conserved, innate immune pattern-recognition receptors that are expressed in different cells and tissues and recognize ligands such as pathogen-associated molecular patterns expressed by microbes or danger-associated molecular patterns expressed by cells during stress or viral infection [5,6]. TLRs are type-1 transmembrane glycoprotein receptors containing the leucine-rich repeat motifs that mediate binding with ligand while the characteristic TLR-IL1R (TIR) cytoplasmic domain binds with downstream adapter proteins. After ligand binding, TLRs undergo a conformational change to homo- or hetero-dimers, followed by recruitment of adapter proteins like myeloid differentiation (MyD)-88 factor or Toll receptor-associated activator of interferon (TRIF) and the intracellular signaling cascade is initiated. TLRs 1, 2, 4, 5, 6, and 10 are

extracellular and basically recognize bacterial products not produced by host while TLRs 3, 7, 8, and 9 are intracellular and are expressed in endosomal and lysosomal compartments where they recognize the released nucleic acids. TLR7 and TLR8 are phylogenetically similar and sense viral pathogens through the recognition of single-stranded and short double-stranded RNAs. Both are expressed in monocytes/macrophages and dendritic cells (DCs) while TLR9 has minimal or no expression in monocytes [7].

The immuno-metabolic regulation is tightly integrated, perhaps because the pathogen- and nutrient-sensing systems are evolutionarily conserved in most species. Several reports support the role of TLRs in non-infectious inflammatory conditions including asthma, inflammatory bowel disease, rheumatoid arthritis, cancer, and obesity/diabetes [8-12]. In obesity, a number of morphological and functional changes occur in the adipose tissue together with expression of soluble factors, called adipokines, which play a role in triggering and propagating metabolic inflammation. The obesity-related changes in the adipose tissue expression of endocytic TLRs, especially TLR7, so far remain unclear. Herein, we report the significantly increased TLR7 expression in the white adipose tissue of individuals with obesity. Moreover, we show that the elevated adipose tissue TLR7 expression

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correlates with activated macrophage markers as well as with local and systemic inflammatory markers.

Subjects and Methods

Study population, anthropometric, and physio-clinical measurements

A total of 49 individuals classified on the basis of body mass index (BMI) as 22 obese (BMI=34.13 ± 2.81 kg/m²), 18 overweight (BMI=28.26 ± 1.20 kg/m²), and 9 lean (BMI=22.61 ± 2.40 kg/m²) were recruited in the study through clinics of Dasman Diabetes Institute, Kuwait. The study exclusion criteria were morbid obesity (BMI≥40 kg/m²), age >65 yrs, immune disorders, pregnancy, malignancy, hyperlipidemia, allergy, asthma, and any other major lung, kidney, liver, or heart disease(s). These individuals underwent a physical examination and essential clinical testing to exclude the presence of T2D by the designated physician at DDI clinics. The clinico-demographic data of study participants are summarized in Table 1. All participants gave written informed consent and the study was approved by institutional research ethics committee.

Height and weight were measured using calibrated portable electronic weighing scales and portable inflexible height measuring bars; the waist circumference was measured using constant tension tape. The whole body composition including percent body fat, soft lean mass and total body water were measured using IOI353 Body Composition Analyzer (Jawon Medical, South Korea). Blood pressure was measured by using Omron HEM-907XL digital automatic sphygmomanometer (Omron Healthcare Inc. IL, USA). BMI was calculated using standard BMI formula i.e. body weight (kg)/ height (m²). Peripheral blood was collected from overnight-fasted individuals and analyzed for fasting glucose, glycated hemoglobin (HbA1c), fasting insulin, and lipid profile. Glucose and lipid profiles were measured using Siemens dimension RXL chemistry analyzer (Diamond Diagnostics, Holliston, MA, USA). Glycated hemoglobin (HbA1c) was measured by using Variant™ device (BioRad, Hercules, CA, USA). Plasma high sensitivity CRP (hsCRP) levels were measured using ELISA kit (Biovendor, USA). Plasma triglycerides were also measured by using commercial kit (Chema Diagnostica, Monsano, Italy). All assays were performed following instructions by the manufacturers.

Table 1: Patients' characteristics and clinical data.

Parameter	Lean	Overweight	Obese
Total number (N)	9	18	22
Male (N)	3	11	11
Female (N)	6	7	11
Age (Yrs.)	41.78 ± 8.09	45.39 ± 11.88	45.55 ± 13.17
Body mass index (kg/m ²)	22.61 ± 2.40	28.26 ± 1.20	34.13 ± 2.81
Percentage of body fat	27.30 ± 5.76	32.35 ± 4.99	39.15 ± 4.24
Glucose (mmol/L)	4.95 ± 0.67	5.57 ± 1.58	5.47 ± 0.79
Cholesterol (mmol/L)	5.30 ± 1.18	4.79 ± 0.71	5.07 ± 1.08
High-density lipoprotein (mmol/L)	1.63 ± 0.50	1.28 ± 0.29	1.15 ± 0.22
Low-density lipoprotein (mmol/L)	3.38 ± 0.96	3.02 ± 0.66	3.31 ± 0.87
Triglycerides (mmol/L)	0.62 ± 0.24	1.11 ± 0.64	1.33 ± 0.84
HbA1c (%)	5.69 ± 0.48	5.88 ± 1.72	5.79 ± 0.63

Collection of subcutaneous adipose tissue samples

The adipose tissue samples (~0.5g) were collected by designated surgeon through the abdominal subcutaneous fat pad biopsy lateral to umbilicus following standard surgical procedure. Briefly, the periumbilical skin area was sterilized by alcohol swab and anesthetized by injecting 2ml of 2% lidocaine locally. A small superficial skin incision (~5mm) was made to collect the subcutaneous fat tissue which was further incised into small pieces, washed in cold sterile phosphate buffered saline, and stored in RNAlater at -80°C until use.

Quantitative real-time RT-PCR

Total RNA was purified by using RNeasy kit (Qiagen, CA, USA) following the manufacturer's instructions. RNA samples (1µg each) were reverse transcribed into cDNA using random hexamer primers and TaqMan reverse transcription reagents (High Capacity cDNA Reverse Transcription Kit; Applied Biosystems, CA, USA). For quantitative real-time RT-PCR, cDNA samples (50ng each) were amplified using TaqMan® Gene Expression MasterMix (Applied Biosystems, CA, USA) and gene-specific 20× TaqMan Gene Expression Assays as follows: (TLR7) Hs01933259_s1; (MyD88) Hs01573837_g1 (IRAK1) Hs01018347_m1; (TRAF6) Hs00371512_g1; (CD68) Hs02836816_g1; (CD11c) Hs00174217_m1; and (GAPDH) Hs03929097_g1 (Applied Biosystems, CA, USA) containing forward and reverse primers and a target-specific TaqMan® minor groove binder (MGB) probe labeled with 6-fluorescein amidite (FAM) dye at the 5' end and non-fluorescent quencher (NFQ)-MGB at the 3' end of the probe, for 40 cycles of PCR reaction using a 7500 Fast Real-Time PCR System (Applied Biosystems, CA, USA). Each cycle included denaturation for 15 sec at 95°C, annealing/extension for 1 min at 60°C which started after uracil DNA glycosylase (UDG) activation (50°C for 2 min) and AmpliTaq Gold enzyme activation (95°C for 10 min). The amplified GAPDH expression was used as internal control to normalize the differences in individual samples and gene expression level of TLR7 relative to controls (lean adipose tissue) was calculated using $^{-2\Delta\Delta Ct}$ method. Relative mRNA expression was shown as fold expression over average of control gene expression. The expression level in control samples was assumed as 1 and data were presented as mean ± SD values.

Statistical Analysis

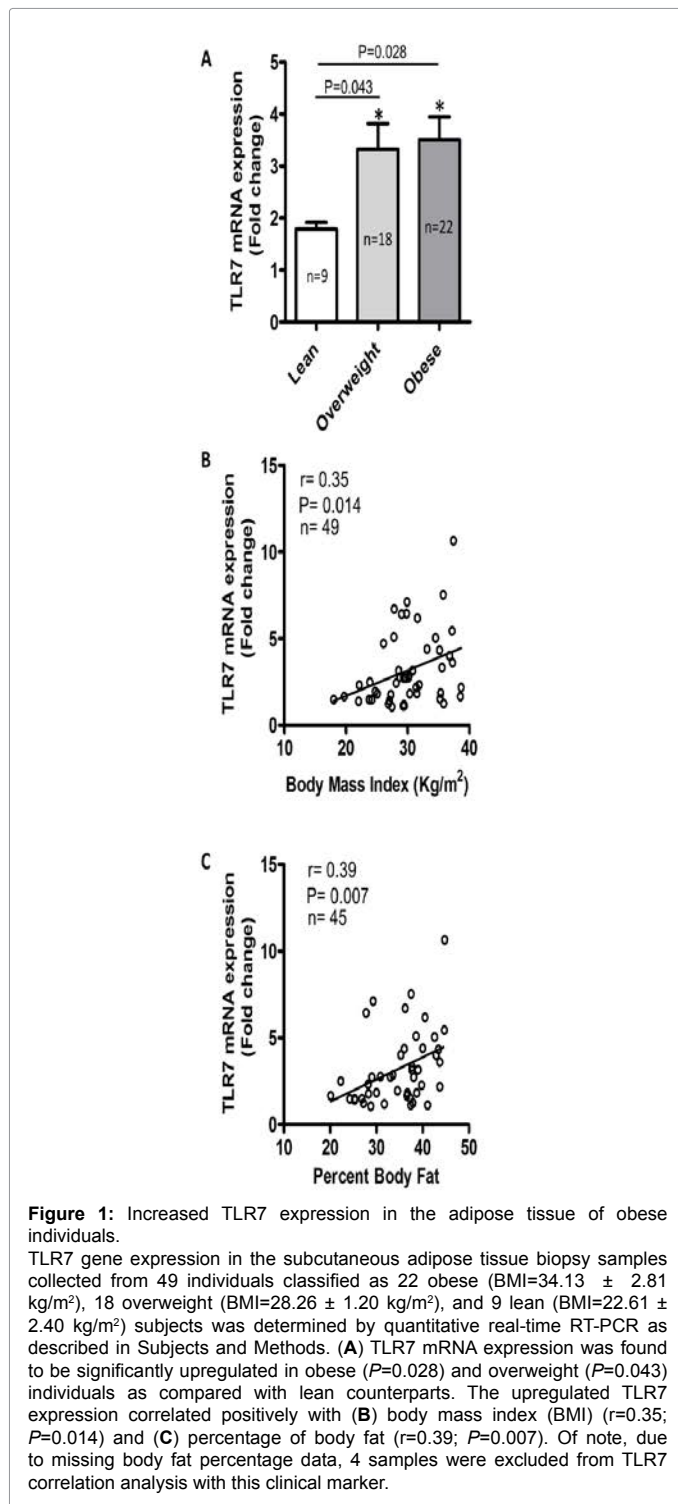
Statistical analysis was performed using GraphPad Prism (La Jolla, CA, USA)/ SPSS19.01 software (IBM SPSS Inc., USA). Data were expressed as mean ± SD values and unpaired Student *t*-test was used to compare group means. Pearson correlation (*r*) test was performed to determine the association between different variables. All *P*-values ≤0.05 were considered statistically significant.

Results

Increased TLR7 expression in the adipose tissue in obesity

TLRs are now recognized as immunometabolic receptors and TLR expression changes may have pathobiological consequences in metabolic conditions such as obesity. The obesity-associated changes in endocytic TLRs, especially TLR7, remain unclear. Therefore, we sought to measure the adipose tissue expression of TLR7 in obese individuals. To this end, we found that TLR7 gene expression in the adipose tissue was significantly upregulated in obese (*P*=0.028) and overweight individuals (*P*=0.043) as compared with lean counterparts (Figure 1A) and this upregulation in TLR7 gene expression correlated positively/significantly with BMI (*r*=0.35 *P*=0.014) (Figure 1B) and percentage of body fat (*r*=0.39 *P*=0.007) (Figure 1C).

TLR7 expression correlates with MyD88 and IRAK1 in the



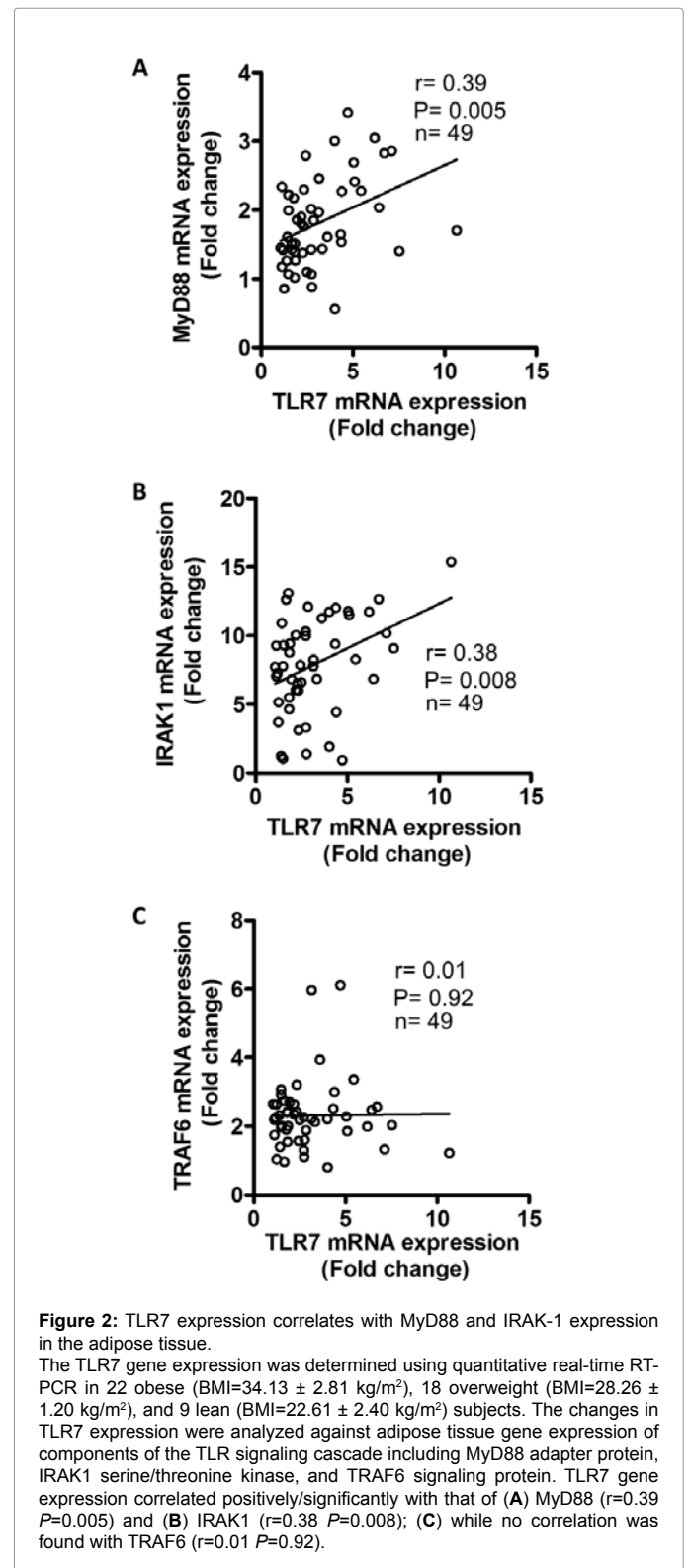
adipose tissue

Next, we asked whether the enhanced adipose tissue TLR7 expression correlated with increased tissue expression of downstream MyD88 adapter protein, IRAK1 serine/threonine kinase, and signal transducer TRAF6 protein. We found that TLR7 gene expression correlated positively/significantly with MyD88 (r=0.39 P=0.005) (Figure 2A) and IRAK1 gene expression (r=0.38 P=0.008) (Figure 2B) but

it did not correlate with TRAF6 expression (r=0.01 P=0.92) (Figure 2C).

TLR7 expression associates positively with ATM markers

In obesity, expanding adipose tissue is infiltrated by immune cells including neutrophils, T/B lymphocytes, NK cells, and more



importantly, monocytes/macrophages called ATMs. The ATMs play a central role in causing adipose tissue inflammation and can be readily identified by CD68/CD11c marker expression. We asked whether the increased TLR7 expression was concordant with the tissue inflammatory state represented by enhanced CD68/CD11c expression from the increased ATM colonization as expected in obesity. To this effect, our data show that the adipose tissue TLR7 expression correlated positively/significantly with CD68 ($r=0.65$ $P<0.0001$) (Figure 3A) and CD11c ($r=0.43$ $P=0.002$) (Figure 3B).

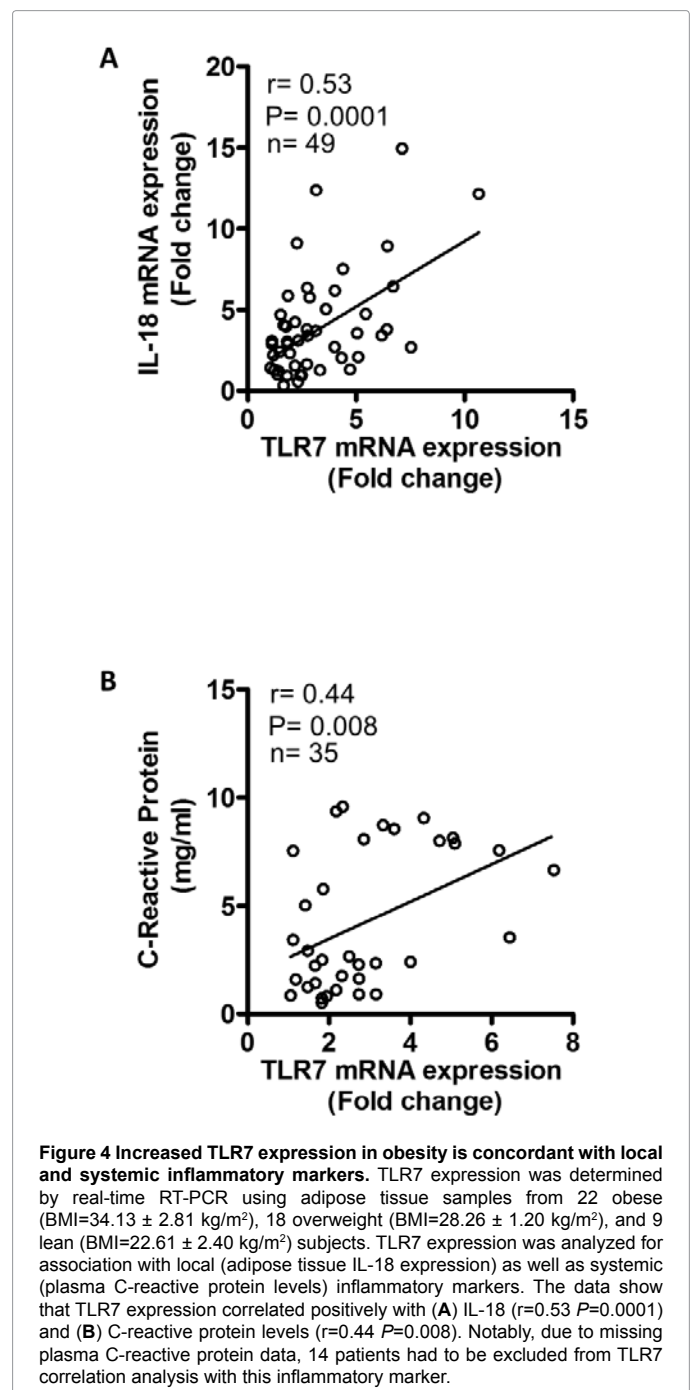
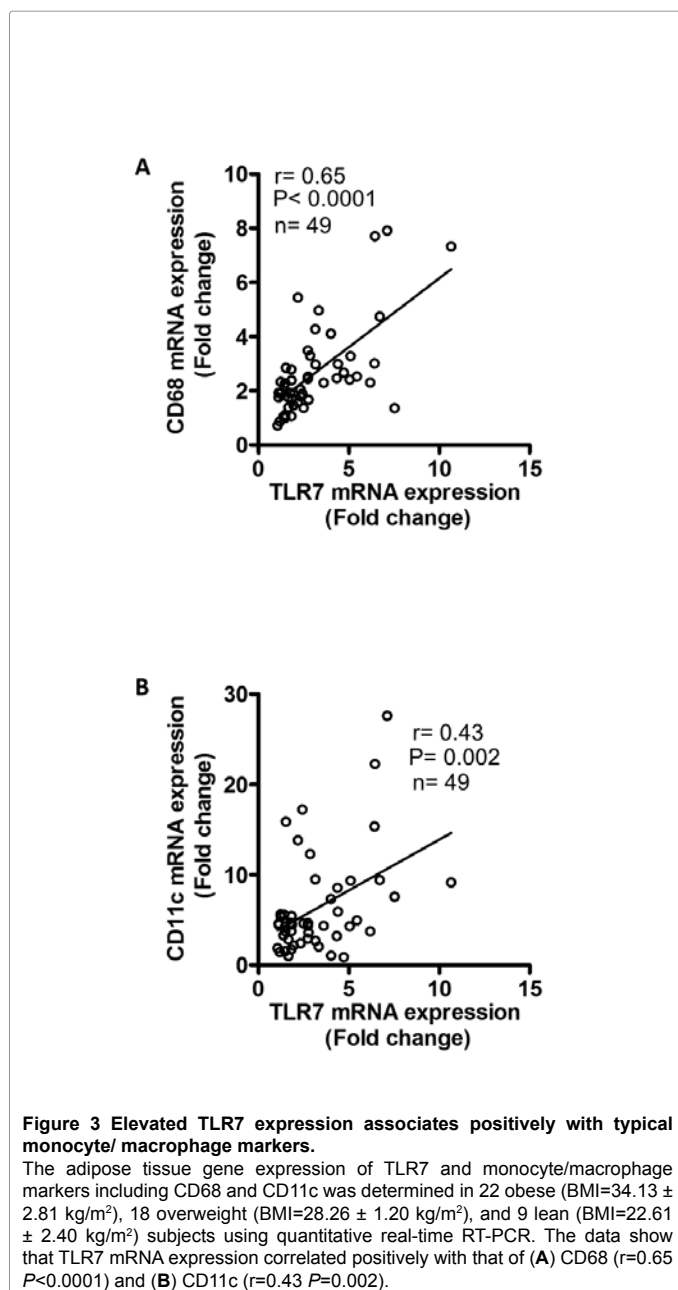
Increased TLR7 expression is concordant with inflammatory signatures

In obesity, adipocytes and ATMs produce proinflammatory cytokines/chemokines that contribute to local and systemic inflammation. We asked whether the TLR7 upregulation in adipose tissue

in obesity had concordance with metabolic disease inflammatory markers, such as IL-18 and CRP. To this end, we found that the adipose tissue TLR7 expression associated positively with IL-18 expression ($r=0.53$ $P=0.0001$) (Figure 4A) and plasma CRP levels ($r=0.44$ $P=0.008$) (Figure 4B).

Discussion

The innate immune surface TLRs, such as TLR2 and TLR4 have emerged as metabolic sensors and regulators of metabolic inflammation. The changes in the expression of endocytic TLRs, especially TLR7 which remains one of the least studied TLR, remain poorly understood. Our data show the upregulated TLR7 expression in the adipose tissue of obese individuals as compared with lean subjects.



TLR7 is expressed on plasmacytoid macrophages and dendritic cells. The upregulation of TLR7 has been reported in various morbid conditions including systemic lupus erythematosus, human pancreatic cancer, and in rheumatic autoimmune disease called Sjogren's syndrome [13-15]. TLR7 expression was reported to be regulated by TLR8 as TLR8^{-/-} mice showed higher expression of TLR7 and increased autoantibody production against ribonucleoproteins and dsDNA that led to lupus development [16]. Interestingly, another study showed that TLR7-mediated lupus was controlled by TLR8 and TLR9 whereby TLR8 regulated TLR7 function in dendritic cells and TLR9 controlled TLR7 response in B cells [17]. In this study, we have determined the global expression of TLR7 in the adipose tissue and thus these changes observed in obesity may relate to its expression on various immune cells, predominantly including the ATMs. We speculate that a cross-regulation among endocytic TLRs 7, 8, and 9 may exist as it was reported to be present between TLR2 and TLR4 expression in the LPS-activated 3T3-L1 cells [18]. Our data further show that the adipose tissue TLR7 gene expression correlated positively/significantly with BMI and percentage of body fat which implies that obesity may be a positive modulator of TLR7 expression in the adipose tissue.

We found that the adipose tissue expression of TLR7 had a positive association with MyD88 and IRAK1 expression. The enhanced expression of TLR7, MyD88, and IRAK1 in the obese adipose tissue indicates a concomitant induction of these TLR-related signaling proteins which may be responsible, at least in part, for chronic low-grade metabolic inflammation which is considered a hallmark of morbid obesity in humans. TLR-mediated responses are predominantly controlled by the MyD88-dependent signaling pathway whereas the TRIF-dependent pathway is used by TLR3 and TLR4. In macrophages and DCs, MyD88 adapter protein recruits IRAK-1, 2, 4, and TRAF6; and this TLR7-MyD88 dependent signaling pathway was found to be involved in immune cell activation and production of type I interferon and inflammatory cytokines by macrophages [19]. However, TLR7 gene expression did not correlate with TRAF6 expression in our study which might be due to the lack of its cellular expression at levels MyD88 and IRAK1 were expressed. TLR7 is the ssRNA sensor in endosomal compartments whereas TRAF6 is critical for signaling cascade involving RIG-like helicases which are cytosolic RNA sensors [20]. It implies that TRAF6 mediates immune responses triggered by cytosolic agonists in a manner different than TLR7 signaling does.

Next, we found that the enhanced TLR7 expression in obese adipose tissue resonated with increased ATM marker expression including CD68 and CD11c. Notably, CD68 is expressed by cells of macrophage lineage including monocytes, giant cells, Kupffer cells, histiocytes, and osteoclasts. It is a typical marker used to assess monocyte/macrophage tissue infiltration under morbid conditions. CD11c is a monocyte/macrophage activation marker. During adipose tissue inflammation, ATMs secrete monocyte chemoattractant protein (MCP)-1 which is a potent driver of the adipose tissue infiltration by circulatory monocytes and sets the stage for chronic low-grade inflammation. Thus, the aggregates of activated macrophages surrounding the degenerating adipocytes in expanding adipose tissue in obesity, known as 'crown-like structures', were reported [21]. Our data showing the increased CD68/CD11c expression in obesity indicate the colonization of adipose tissue by inflammatory immune cells, especially monocytes/macrophages, which is in agreement with previous reports [22,23].

In obesity, several bioactive proteins including cytokines/chemokines and hormones, collectively called as adipokines, are expressed in the expanding adipose tissue and these adipokines act via autocrine/paracrine mechanisms for crosstalk between adipocytes and

ATMs. The white adipose tissue is a site for excessive energy storage and is also an active endocrine organ that secretes adipokines [24]. We found that TLR7 gene expression correlated positively with local and systemic inflammatory markers in obesity including IL-18 and CRP, respectively. Of note, IL-18 is a proinflammatory cytokine that is predominantly expressed by macrophages and is an important mediator involved in acute inflammatory responses while CRP is an acute phase protein of the hepatic origin, and is considered to be a typical systemic inflammatory marker indicating the release of inflammatory mediators in the circulation. Macrophages as well as adipocytes may act as both the source and target of proinflammatory signals including IL-18 [25]. IL-18 was shown to have proinflammatory effects in the adipose tissue via the release of IL-8 and IL-1 β in a TNF- α -dependent mechanism in monocytes [26]. Such interactions among various adipokines in the adipose tissue may trigger the local as well as systemic inflammatory responses. We found that the circulatory CRP levels were also elevated in obesity. The present data showing the increased IL-18/CRP expression in obesity are in agreement, at least in part, with previous reports [27-33].

Our data further indicate that IL-18/CRP expression correlated positively/significantly with TLR7 expression in the adipose tissue. The TLR augmentation may have pathobiological consequences, especially the induction of inflammatory response, as the saturated free fatty acids in obesity/T2D were reported to stimulate the TLR-mediated cytokine production [34,35]. The upregulated cytokines/chemokines and TLR expression in obesity were linked to insulin resistance [36,37] which may explain as to why obese individuals are more prone to developing insulin resistance. Although, increased expression of surface TLRs has been reported in obesity/T2D [12,35,38], our data point to the upregulated expression of endosomal TLR7 and its association with inflammatory signatures in metabolic disease. Besides, these obesity-related TLR7 changes have been investigated in the subcutaneous adipose tissue which is easily accessible by transcutaneous biopsy for clinical studies. Further studies involving larger cohorts with or without T2D as well as expression analysis of other endosomal TLRs will be required to validate and extend these preliminary findings.

In conclusion, we show that TLR7 expression was significantly upregulated in the subcutaneous adipose tissue of obese individuals as compared with lean counterparts. Based on consensus with inflammatory signatures, TLR7 expression may be considered a novel inflammatory marker in the adipose tissue in obesity. This correlative study also bears clinical significance whereby the interventions attenuating TLR7 expression in the adipose tissue may be desirable to improve the metabolic complications.

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